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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/017,306	12/13/2001	Kevin P. Baker	GNE.2830P1C66	7268

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EXAMINER	
BUNNER, BRIDGET E	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 04/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/017,306	BAKER ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 January 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32,33,38 and 44-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32,33,38 and 44-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *31 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/26/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 26 January 2005 has been entered in full. Claims 1-31, 34-37, and 39-43 are cancelled. Claims 32-33, 38, 44, and 46 are amended.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 32-33, 38, and 44-47 are under consideration in the instant application.

Withdrawn Objections and/or Rejections

1. The objections to the specification at pg 2 of the previous Office Action (26 July 2004) are *withdrawn* in view of the amended specification and title (26 January 2005).

2. The rejections to claims 28-34, 36-37, and 41-47 under 35 U.S.C. 112, second paragraph, as set forth at pg 13-14 of the previous Office Action (26 July 2004) are *withdrawn* in view of the amended claims and cancelled claims (26 January 2005).

3. The rejections to claims 28-33 under 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph (enablement) as set forth at pg 2-13 of the previous Office Action (26 July 2004) are *withdrawn in part* in view of cancelled and amended claims (26 January 2005). Please see section on 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph, below.

4. The rejection to claims 28-32 and 41-47 under 35 U.S.C. § 112, first paragraph (written description) as set forth at pg 11-13 of the previous Office Action (26 July 2004) is *withdrawn in part* in view of the amended and cancelled claims (26 January 2005). Please see section on 35 U.S.C. § 112, first paragraph, below.

5. The rejection to claims 28-31 and 41-47 under 35 U.S.C. § 102(a) as set forth at pg 15 of the previous Office Action (26 July 2004) is *withdrawn* in view of the amended and cancelled claims (26 January 2005). The Ruben et al. patent no longer teaches the polypeptide variants recited by the instant claims.

6. The supplemental information disclosure statement filed on 26 January 2005 has been considered.

New Claim Objections

7. Claim 38 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 38 recites the isolated nucleic acid of claim 33 comprising the nucleic acid sequence of SEQ ID NO: 375. However, claim 33 also recites an isolated nucleic acid comprising the nucleic acid sequence of SEQ ID NO 375.

Claim Rejections - 35 USC § 101 and 35 USC § 112

8. Claims 32-33, 38, and 44-47 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility. Novel biological molecules lack well established utility and must undergo extensive experimentation. The basis for this rejection is set forth for claims 28-47 at pg 2-11 of the previous Office Action (26 July 2004).

Specifically, claims 32-33, 38, and 44-47 are directed to an isolated nucleic acid having at least 99% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 375.

The claims also recite an isolated nucleic acid comprising the nucleic acid sequence of SEQ ID NO: 375. The claims also recite a vector and host cell.

Applicant's arguments (26 January 2005), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

(i) Applicant asserts that the adipocyte glucose/FFA uptake assay (Example 149) is relied upon for support of patentable utility. Applicant explains that the glucose/FFA assay is designed to determine whether a polypeptide is capable of modulating (either positively or negatively), the uptake of glucose or free fatty acids in adipocyte cells. Applicant cites Tafuri et al. (Endocrinology 137(11) : 4706-4712, 1996), Sandouk et al. (endocrinology 133(1): 352-359, 1993), Goldwaser et al. (J Biol Chem 274(37): 26617-26624, 1999), Mueller et al. (Endocrinology 139(2) : 551-558, 1998), and Mueller et al. (Obesity Research 8(7): 530-539, 2000) to support the assertion that increasing glucose uptake by adipocyte cells is a hallmark of a number of therapeutically effective agents. Applicant argues that one of skill in the art would have reasonably accepted that various compounds, such as PRO1760, that are capable of modulating glucose uptake, have a substantial, practical, real-life utility. Applicant contends that a variety of real-life utilities, such as treatments for glucose uptake related diseases, including obesity and diabetes, are envisioned for PRO1760 based on the glucose/FFA uptake assay results disclosed therein. It is noted that Applicant reviews the legal standard for utility at pg 8-9 of the Response.

Applicant's arguments have been fully considered but are not found to be persuasive. The specification of the instant application teaches that PRO1760 is positive as *inhibitor* of glucose and FFA uptake by adipocytes (pg 512, lines 9-10). Applicant's agent even reiterates

this finding by stating at pg 10 of the Response, "As PRO1760 resulted in less then 0.5 the uptake of insulin control, PRO1760 tested positive as an inhibitor of glucose/FFA uptake in adipocyte cells". However, each of the 5 references cited by Applicant teach that the agents utilized in the assays *enhance* glucose uptake by adipocyte cells, not inhibit glucose uptake as asserted by the instant specification. As discussed in the previous Office Action of 26 July 2004, disorders, such as obesity, diabetes, and hyper- or hypo-insulinemia have reduced glucose entering adipocyte cells. For example, Khan et al. (Diabetologia 45: 1475-1483, 2002; especially pg 1475, 1st full paragraph) teach that "type II (non-insulin-dependent) diabetes mellitus is a clinical disorder of sugar and fat metabolism caused by an inability of insulin to promote sufficient glucose uptake into adipocyte tissue and striated muscle and to prevent glucose output from the liver". Therefore, as emphasized by Tafuri et al., Sandouk et al., Goldwaser et al., Mueller et al. 1998, and Mueller et al. 2000, one skilled in the art would want to enhance glucose uptake into adipocyte cells. However, it is noted again that Applicant asserts the PRO1760 polypeptide encoded by the claimed nucleic acid inhibits glucose uptake in adipocyte cells. If one skilled in the art were to administer the PRO1760 polypeptide of the instant application to a patient with obesity, diabetes, and hyper- or hypo-insulinemia, the PRO1760 polypeptide would exacerbate the condition. Given the paucity of information, the data do not support the implicit conclusion of the specification that PRO1760 would be useful for the therapeutic treatment of disorders where the inhibition of glucose uptake by adipocytes would be beneficial including, for example, obesity, diabetes or hyper- or hypo-insulinemia. The proposed use of the claimed PRO1760 polypeptides and polynucleotides are simply starting points for further research and investigation into potential practical uses of the polypeptides.

Furthermore, Tafuri et al., Sandouk et al., Goldwaser et al., Mueller et al. 1998, and Mueller et al. 2000 teach different methodologies for the measurement of glucose uptake in adipocyte cells as compared to the glucose assay of the instant specification. For instance, the instant specification teaches that "in a 96 well format, PRO polypeptides to be assayed are added to primary rat adipocytes, and allowed to incubate overnight. Samples are taken at 4 and 16 hours and assayed for glycerol, glucose and FFA uptake. After the 16 hour incubation, insulin is added to the media and allowed to incubate for 4 hours. At this time, a sample is taken and glycerol, glucose and PFA uptake is measured. Media containing insulin without the PRO polypeptide is used as a positive reference control" (pg 512, lines 1-4). However, Sandouk et al. teach that 3T3-F442A cell monolayers were rinsed with PBS and incubated with assay medium for 15 min. Then, 0.5 μCi D-[U-^{14}C]glucose was added for 15 min. After this incubation, the medium was aspirated, cells were rinsed, solubilized, neutralized, and counted for radioactivity (pg 353, col 1, first full paragraph). Mueller et al. 2000 disclose that aliquots of adipocytes are incubated with different concentrations of either metformin or vanadium at 24, 48, 72, and 96 hours with or without insulin (pg 532, the bottom of col 1 through col 2). Additionally, the papers cited by Applicant report resulting numbers for the various samples of the glucose uptake assays. None of the references utilize the stimulatory and inhibitory scale disclosed in the specification (pg 512, lines 4-6). The instant specification does not report any specific cell numbers or statistical differences and there is no indication in the specification as to statistically how much the PRO1760 inhibited glucose uptake as compared to control.

In conclusion, the PRO1760 polynucleotide, polypeptide, and antibody of the instant application (SEQ ID NOs: 375 and 376, respectively) are not supported by either a credible,

specific and substantial ("real-world") asserted utility or a well-established utility. The polynucleotide, polypeptide, and antibody do not have a substantial utility because basic research is required to study the properties and activity of the polynucleotide that encodes the polypeptide of SEQ ID NO: 376. Until some actual and specific significance can be attributed to the protein identified in the specification as PRO1760, the instant invention is incomplete. In the absence of knowledge of the biological significance of this protein, there is no immediately obvious patentable use for it. Since the instant specification does not disclose a "real world" use for PRO1760 then the claimed invention is incomplete and, therefore, does not meet the requirements of 35 U.S.C. § 101 as being useful.

9. Claims 32-33, 38, and 44-47 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. The basis for this rejection is set forth for claims 28-47 at pg 8 of the previous Office Action (26 July 2004).

Applicant's arguments (26 January 2005), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant states that a credible, substantial, and asserted utility has been disclosed above for the PRO1760 polynucleotide and polypeptide. Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, since Applicant has not provided evidence to demonstrate that the PRO1760 polypeptide has a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed

invention. It is noted that the instant specification is required to teach one skilled in the art how to make and use the PRO1760 polypeptide and polynucleotide.

10. However, even if the claimed invention is eventually deemed to have a credible, specific and substantial asserted utility or a well established utility, claims 32 and 44-47 would remain rejected under 35 U.S.C. § 112, first paragraph. The basis for this issue is set forth at pg 8-11 of the previous Office Action (26 July 2004).

Applicant's arguments (26 January 2005), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant asserts that claim 32 is amended to recite a functional limitation that the polypeptide "inhibits the uptake of glucose or FFA (free fatty acid) by adipocyte cells". Applicant argues that since the claimed genus is now characterized by a combination of structural and functional features, any person of skill would know how to make and use the invention without undue experimentation based on the general knowledge in the art at the time the invention was made. Applicant cites *In re Certain Limited-charge cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), aff'. sub nom., *Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Circ. 1985) to emphasize the fact that experimentation may be complex does not necessarily make it undue.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, as discussed in the previous Office Action, certain positions in the polypeptide sequence are critical to the protein's structure/function relationship, e.g., such as various sites or regions directly involved in binding, activity, and in providing the correct three-dimensional spatial orientation of binding and active sites. However, Applicant has provided little or no

guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the DNA and protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. A large quantity of experimentation would be required by the skilled artisan to generate the infinite number of derivatives recited in the claims and screen the same for activity. As was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). Furthermore, recitation of the phrase "wherein the polypeptide inhibits the uptake of glucose or FFA (free fatty acid) by adipocyte cells" in claim 32 is not adequate to describe the PRO1760 polynucleotide or all possible variants that have at least 99% homology to the PRO1760 polynucleotide, since there was no reduction to practice to support the amended claims.

Additionally, it is noted that the fact pattern of the case cited by the Applicant (*In re Certain Limited-Charge Cell Culture Microcarriers*) and the fact pattern of the instant rejection are significantly different, and the court decision is not binding with regard to the instant rejection. For example, in *Certain Limited-Charge Cell Culture Microcarriers,* the main issue was patent validity and unfair competition. The patented claims are drawn to microcarrier beads for cell culture and a method of using the microcarriers for cell culture, not polynucleotide

variants. Evidence has been cited on the record establishing that there is little guidance in the specification regarding which structural features are required in order to provide activity and that the prior art discloses the unpredictability of the effects of mutation on protein structure and function.

Proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

11. Claims 32 and 44-47 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is set forth for claims 28-32 and 41-47 at pg 11-13 of the previous Office Action (26 July 2004).

Applicant's arguments (26 January 2005), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant contends that claim 32 is amended to recite a functional limitation that the polypeptide "inhibits the uptake of glucose or FFA (free fatty acid) by adipocyte cells".

Applicant argues that it is no longer true that the claims are drawn to a genus of polynucleotides defined by sequence identity alone. Applicant submits that this biological activity, coupled with a well-defined, and relatively high degree of sequence identity are believed to sufficiently define the claimed genus, such that one skilled in the art would readily recognize that the Applicant was in possession of the invention.

Applicant's arguments have been fully considered but are not found to be persuasive. Applicant has not described or shown possession of all nucleic acids 99% homologous to SEQ ID NO: 375, that still retain the function of SEQ ID NO: 375. Nor has Applicant described a representative number of species that have 99% homology to SEQ ID NO: 375, such that it is clear that they were in possession of a genus of polynucleotides functionally similar to SEQ ID NO: 375. As discussed in the previous Office Action (26 July 2004), even one skilled in the art could not envision the detailed chemical structure of all or a significant number of encompassed PRO1760 polynucleotides, and therefore, would not know how to make or use them. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of making. The claimed product itself is required. Recitation of the phrase "wherein the polypeptide inhibits the uptake of glucose or FFA (free fatty acid) by adipocyte cells" in claim 32 is not adequate to describe the PRO1760 polynucleotide variants that have 99% homology to the PRO1760 polynucleotide, since there was no reduction to practice to support the amended claims. Applicants made no variant polynucleotides or polypeptides, and as recited in the current Written Description Guidelines, Applicants must have invented the subject matter that is claimed and must be in "possession" of the claimed genus (Federal Register, 2001, Vol. 66, No. 4, pages 1099-1111, esp. page 1104, 3rd column).

Conclusion

No claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 8:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Elizabeth C. Kemmerer

BEB
Art Unit 1647
04 April 2005

ELIZABETH KEMMERER
PRIMARY EXAMINER